



# Armed Forces College of Medicine

## AFCM



# Myasthenia Gravis

## Recorded by

**Noha Samir Abdel Latif**

**Lecturer of Pharmacology**

# INTENDED LEARNING OBJECTIVES (ILO)



**By the end of this lecture the student will be able to:**

**1- Classify the drugs used in treatment of myasthenia gravis**

**2- Explain the mechanism of action and adverse effects of drugs used in treatment of myasthenia gravis**



# Introduction

- **Myasthenia gravis (MG)** is an autoimmune disorder affecting neuromuscular transmission, Leading to generalized or localized muscle weakness characterized by easy fatigability, Severe disease may affect all the muscles, including those necessary for respiration.
- **It is due to production of auto-antibodies against acetylcholine receptors** (antibodies against Motor End Plate (M.E.P.). In this disease, antibodies are produced against the main immunogenic region found on  $\alpha 1$  subunits of the nicotinic receptor channel complex. Antibodies are



# Introduction

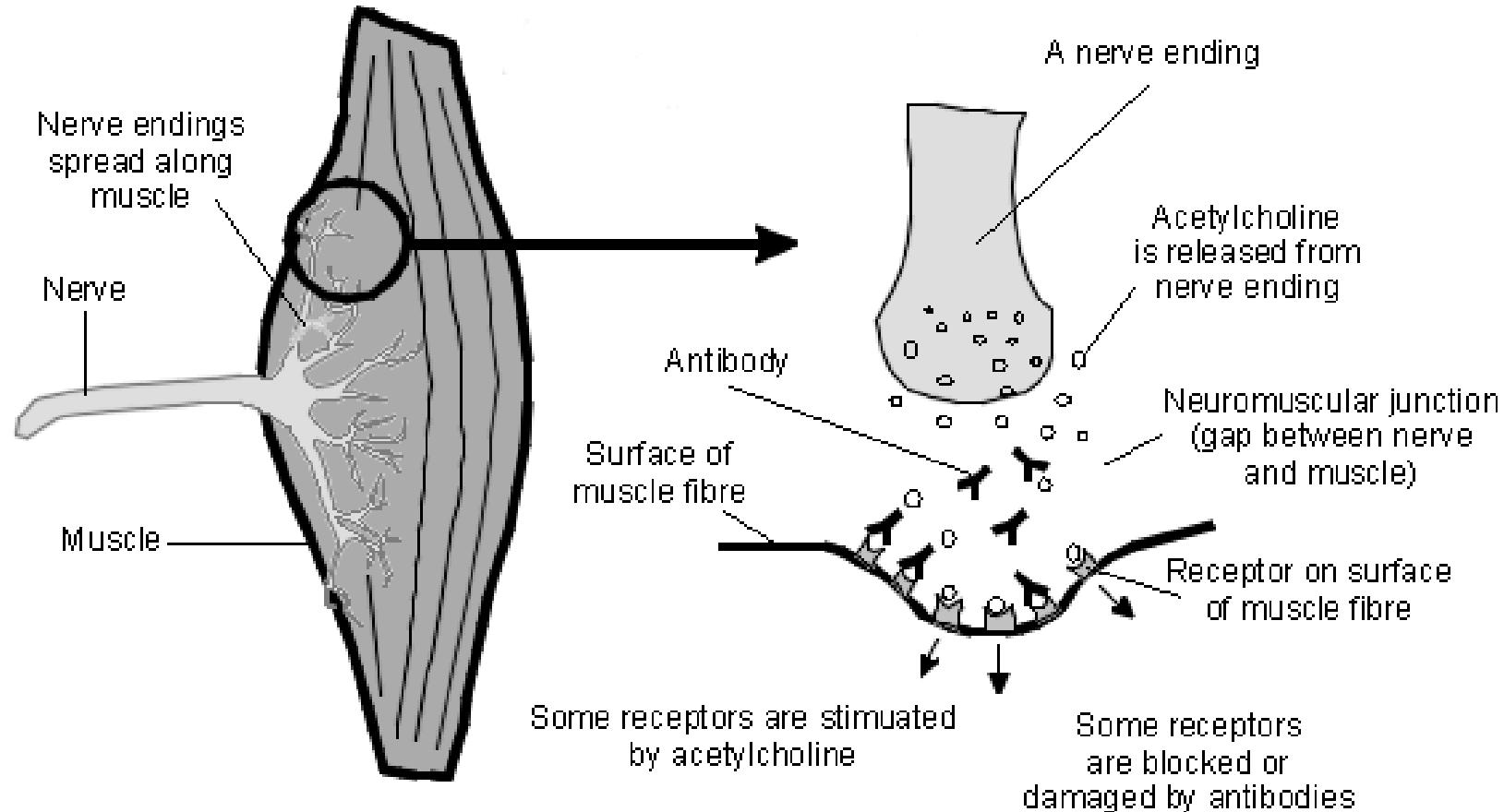
**The antibodies reduce nicotinic receptor function by:**

- (1) Cross-linking receptors, a process that stimulates their internalization and degradation
- (2) Causing lysis of the postsynaptic membrane
- (3) Binding to the nicotinic receptor and inhibiting function.

Frequent findings are ptosis, diplopia, difficulty in speaking and swallowing, and extremity weakness



# Introduction

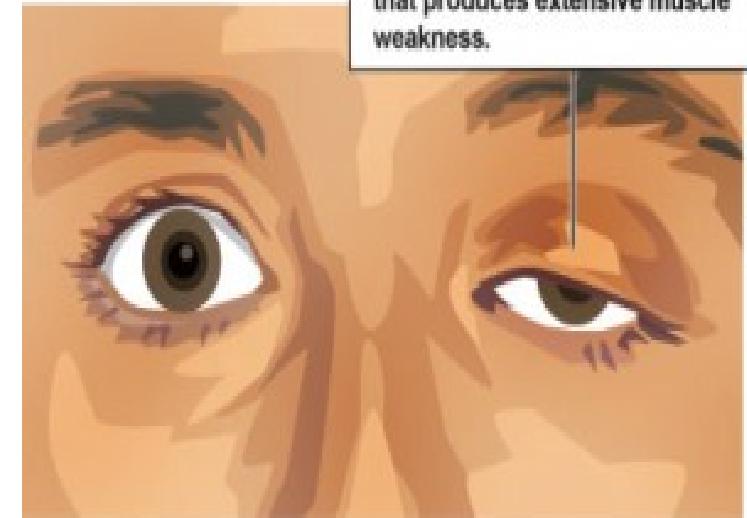




# Clinical Picture

- Fatigue with muscle use
- Double vision, droopy eyelids, trouble swallowing/chewing
- Facial weakness
- Shortness of breath
- **Myasthenic crisis** is a complication of myasthenia gravis characterized by worsening of muscle resulting failure that requires intubation and mechanical ventilation

A drooping eyelid, is the most frequent early sign of myasthenia gravis, a disease that produces extensive muscle weakness.



# Cholinergic and Myasthenic crisis



Cholinergic crisis	Myasthenic crisis
<b>Due to:</b> <b>Excessive ChE inhibition (over dose) → Maintained depolarization at N-M junction.</b>	<b>Due to:</b> <b>Insufficient treatment with: Choline esterase inhibitors.</b>
<b>I.V Edrophonium → produces <b>more weakness.</b></b>	<b>I.V Edrophonium → produces <b>muscle improvement.</b></b>

# To differentiate between cholinergic and myasthenic crisis:

**Edrophonium IV** is used.

- It is a **Reversible** choline esterase inhibitor.
- Shortly acting** (duration 5 min).

**Also**, Edrophonium can be used as a pharmacological test in **diagnosis** of myasthenia gravis → improvement of symptoms (**Edrophonium IV + Atropine**).

# Treatment of Myasthenia Gravis



## 1- Anticholine esterases:

- ❖ **Neostigmine** : is a reversible cholinesterase inhibitor □ inhibits the degradation of Acetylcholine(Ach) □ Accumulation of Ach.
  - ↑ Acetylcholine concentration□ stimulate both Nicotinic (Nm in N-M junction) & Muscarinic receptors.
  - ↑ **skeletal muscle power, used orally in treatment of myasthenia gravis.**

# **Neostigmine Substitutes**

- ❖ **Pyridostigmine**
- ❖ **Ambenonium**



## **Reversible cholinesterase inhibitor**

Preferred to neostigmine in myasthenia gravis :

- More specific.
- Longer duration of action.
- Fewer visceral side effects.
- ↑ selectivity on skeletal muscles compared to it.

# Neostigmine Substitutes



Edrophonium	Pyridostigmine & Ambenonium
<b>Selectivity:</b> muscle	Skeletal
<b>Duration:</b> 5 min	Short
<b>Uses:</b>  M.gravis  myasthenic crisis due to (improve patient)  cholinergic crisis	1- Diagnosis of  2- ttt of under ttt  3- Diagnosis of  due to over ttt

# Treatment of Myasthenia Gravis



## 2- Atropine:

Atropine causes reversible competitive blockade of the actions of Ach at muscarinic receptors (**non-selective muscarinic receptors blocker**).

Atropine is added to block the unwanted side effects of reversible anticholine esterases which result from stimulation of muscarinic receptors by the accumulated Acetylcholine.

# **These unwanted side effects are:**

## **- Muscarinic:**

Bradycardia, hypotension, bronchospasm, miosis, vomiting, diarrhea, increase secretions (sweating, salivation, bronchial and lacrimation).

## **- Nicotinic:**

Sk. Muscle twitches, eye lid, facial, trunk.

# Treatment of Myasthenia Gravis



## 3- Adjuvant ttt:

- a- **Ephedrine:** Potentiates Neostigmine  
(VD of skeletal BV + facilitate NM transmission)
- b- **Caffeine:** Potentiates Neostigmine  
(Direct stimulation of ms)

## **4- Others:**

- a- Immunosuppressants as corticosteroids :** Decrease antibody formation.
- b- Plasmapharesis** to wash acetylcholine receptor antibodies from the circulation.
- c- Thymectomy.**

# Immunomodulating therapy



## Corticosteroids

-Corticosteroids can suppress the immune system in several ways.

-Prednisone has been shown to reduce acetylcholine receptor antibody levels

## Azathioprine

-Azathioprine (Imuran) is an antimetabolite that blocks T lymphocytes proliferation.

-Azathioprine is used most often in patients who have relapsed while on prednisone or as a steroid-sparing agent in patients who have been taking prednisone for long periods of time

# Immunomodulating therapy



## Cyclosporine

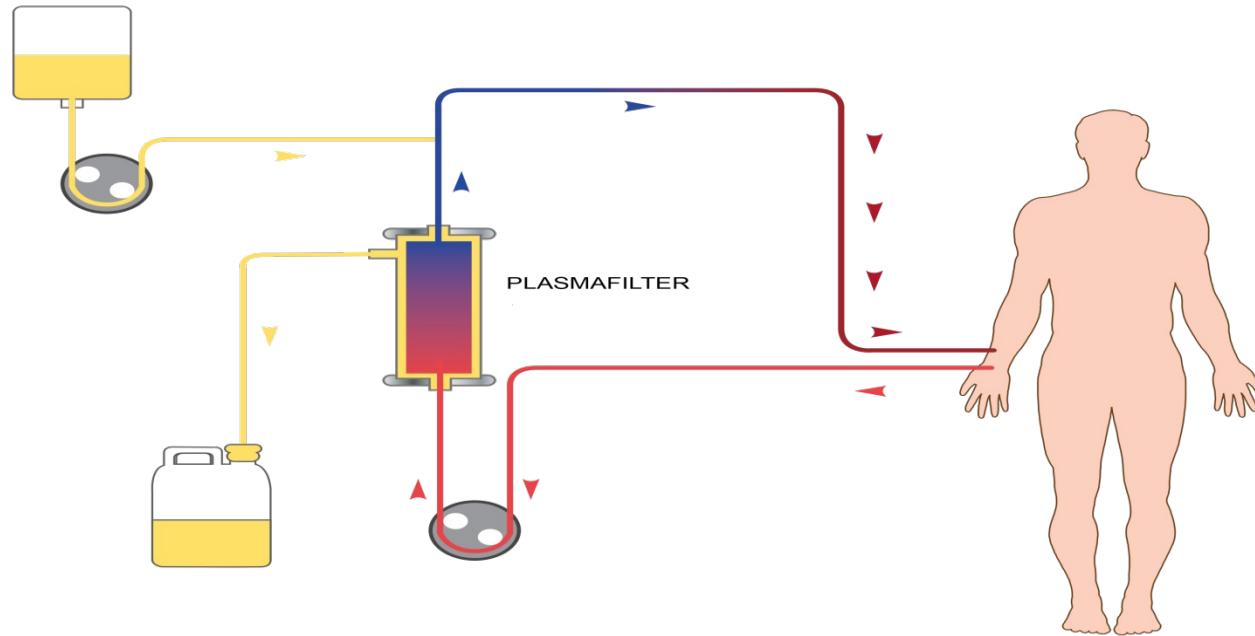
- Cyclosporine (Sandimmune, Neoral), a drug designed to prevent rejection in organ transplantation patients
- Inhibits T cell proliferation by inhibiting IL-2 secretion.

## Mycophenolate Mofetil

- MM (CellCept) is another immunosuppressive agent used in organ transplantation.
- By selectively blocking purine synthesis it suppresses both T- and B-cell proliferation.

## Intravenous Immunoglobulin

# Plasmapharesis



- Plasmapheresis, a procedure that removes acetylcholine receptor antibodies from the circulation.
- Improvement following plasmapheresis occurs within a few days, much faster than for other immunomodulating therapies.
- Plasmapheresis is an established therapy for patients in myasthenic crisis

# **Drugs contraindicated in Myasthenia Gravis**



- 1-Skeletal muscle relaxants**
- 2-Aminoglycosides**
- 3-Lithium**
- 4-Beta blockers e.g. propranolol**
- 5-Anti-arrhythmics e.g. quinidine & lidocaine**

# Summary of Myasthenia Gravis



Autoimmune disease characterized by muscle weakness & easy muscle fatigability due to formation of antibodies against Motor End Plate (M.E.P.)

## Diagnosis:

Edrophonium IV + Atropine

## Treatment:

- 1- Antich. esterase:** Neostigmine or pyridostigmine
- 2- Atropine:** block unwanted muscarinic actions.
- 3- Adjuvant ttt:** a- Ephedrine: b- Caffeine
- 4- Others:** a- Cortisol      b- Plasmapharesis      c- Thymectomy

# Lecture Quiz



**1)- The following drug is contraindicated in myasthenic patients:**

- a- Aminoglycoside
- b- Ephedrine
- c- Caffeine
- d- Cortisol

**a- Aminoglycoside**

# Lecture Quiz



**2)- The following drug is used in the diagnosis of myasthenic patients:**

- a- Pyridostigmine
- b- Ambenonium
- c- Edrophonium
- d- Lithium

**c- Edrophonium**

# Lecture Quiz



**3)- All of the following drugs are used in the treatment of myasthenic patients EXCEPT:**

- a- Pyridostigmine
- b- Neostigmine
- c- Atropine
- d- Curare

**d- Curare**

# SUGGESTED TEXTBOOKS



- 1- Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer
  
- 2- Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.

# THANK YOU

